CANCER IMMUNOTHERAPY IN VETERINARY ONCOLOGY

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Overview

- Cancer and the immune system
- Introduction to immunotherapy
  - Non-specific vs. specific
- Biologic response modifiers
- Recombinant cytokine therapy
- Cancer vaccines
  - Melanoma
  - Osteosarcoma
- Monoclonal antibodies
  - Lymphoma
- Metronomic chemo
- Future directions
Cancer and the Immune System

- Spontaneous cancer remission
  - Histiocytomas, TVT
- Immune infiltrate in solid tumors
  - Canine MGTs
- Cancer in the immunosuppressed
  - Diminished immune surveillance
- Immunomodulator-induced cancer remissions
- Infections, cancer, and improved survival
  - Limb sparing procedures in dogs with OSA
Cancer and the Immune System

- Immune evasion by cancer
  - Immunosuppressive cytokines
    - IL-10
    - TGF-β
  - Regulatory T cells
  - Myeloid-derived suppressor cells
  - Down regulation of MHC Class I
  - Attenuation of B7
Cancer and the Immune System

- Immune evasion by cancer
Immunotherapy

- **Definition**: treatment of a disease by altering the host’s immune response

- **Non-specific immunotherapy**
  - TLR and NLR activation
  - NK cells and macrophages/monocytes
  - Little memory

- **Specific immunotherapy**
  - Vaccines, monoclonal antibodies
  - Effector T cells
  - Memory
Biologic response modifiers

- Non-specific immunotherapy
- Augmented immune response through antigen stimulation
- Coley’s toxins
  - *Streptococcus pyogenes*
  - *Serratia marcesens*
Biologic response modifiers

- Bacillus Calmette-Guérin (BCG)
  - Live, attenuated *Mycobacterium bovis*
  - Intravesicular bladder instillation
  - Canine cancer
    - Mammary carcinomas
    - Osteosarcoma
    - Lymphoma
  - LDI-100 (BCG + hCG) in canine mast cell tumors
Biologic response modifiers

- **L-MTP-PE**
  - Liposomal-encapsulated muramyl tripeptide phosphatidylethanolamine
  - Synthetic analog of peptidoglycan cell wall
  - NLR-agonist
  - Potent macrophage stimulator
- **Veterinary medicine**
  - Osteosarcoma*
  - Hemangiosarcoma
  - Anti-metastatic properties
Biologic response modifiers

- Imiquimod
  - Toll-like receptor 7 agonist
  - Primary mechanism:
    - Induction of IFNα and TH1 response
  - Activation of macrophages/monocytes
  - Neutrophil chemotaxis
  - B cell activation
  - Bowen’s disease in cats
  - Actinic keratosis and solar-induced SCC in dogs
Recombinant cytokine therapy

- IL-2
  - Released by T cells
    - Clonal expansion of T cells
    - NK cell response
  - Canine pulmonary carcinoma
    - Aerosolization
  - IL-2 vaccine
    - Europe
    - Feline fibrosarcomas
    - In combo with surgery and RT
    - Longer time to disease recurrence compared to historic control
Cancer Vaccines

[Image of three vials with green, pink, and purple ribbons]
Cancer Vaccines

- Malignant melanoma
  - Oncept™ melanoma vaccine
  - Xenogenic DNA vaccine
    - Human tyrosinase*
  - Transdermal administration
    - 4 initial doses q 2 weeks, then q 6 months
  - Immunogenicity
    - Tyrosinase Ab production
    - Demonstration of a specific T cell response
Cancer Vaccines

• DNA vaccines and the immune response
Cancer Vaccines

- **Oncept™ melanoma vaccine**
  - Disputed efficacy
    - Bergman et al. (2003) and Liao et al. (2006) → favorable response, MST = 389 d
      - n=9, uncontrolled
    - Groesenbaugh et al. (2011) → apparent survival benefit
      - n=58, use of historical controls, high rate of patient censorship
    - Ottnod et al. (2013) → no survival benefit
      - n=22 vaccinees, n=23 control dogs
    - Treggiari et al (2016) → no survival benefit
      - No control group; other adjuvant therapy was not standardized

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**Figure 1. Increased Survival Times in Dogs Treated with ONCEPT™**

[Graph showing survival probability comparison between dogs treated with ONCEPT and surgery alone.](image-url)
Cancer Vaccines

- Osteosarcoma
  - Phase I clinical trial with DNA vaccine

Immunotherapy with a HER2-Targeting *Listeria* Induces HER2-Specific Immunity and Demonstrates Potential Therapeutic Effects in a Phase I Trial in Canine Osteosarcoma

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Cancer Vaccines

- Osteosarcoma
  - Attenuated, live *Listeria monocytogenes* expressing human HER2
  - Dose-escalation phase I clinical trial
  - n=18 dogs
    - Vaccinated with 3 doses q 3 weeks, then q 4-6 months
    - Dogs received “standard of care” prior to vaccination
    - Dogs had HER2+ tumors
  - Minimal toxicity noted
  - Reduced incidence of metastatic disease and improved overall survival
    - *compared to historic controls*
Cancer Vaccines

- Listeria vaccine technology
Cancer Vaccines

- Immune response to HER2 vaccine
  - T cell response
    - IFN\(\gamma\) release in response to exposure to HER2
    - Identified early and late responders within group
    - No dose-dependent effect on immune response
  - Dogs that developed IFN\(\gamma\) response to HER2 at \(> 6\) months tended to have better long term survival
Monoclonal antibodies
Monoclonal antibodies

- Monoclonal antibody generation
Monoclonal antibodies

- Canine lymphoma
  - B cell lymphoma
    - CD20 mAb
    - Use in combo with CHOP → longer remission time and overall survival
    - Use in combo with doxorubicin → improved progression free survival
  - T cell lymphoma
    - CD52 mAb
    - Preliminary results do not reveal survival benefit
- Reduced manufacturing
Metronomic chemotherapy

- Combination therapy
  - Low-dose alkylating agent
  - NSAID
- Anti-angiogenic
- Immunomodulatory
  - Down regulation of regulatory T cells
- Soft tissue sarcomas
- Hemangiosarcoma
- Metastatic sarcomas and carcinomas

![Graphs showing changes in Treg cells over time.](image-url)
Future directions

- Modified T cell transfer
  - CAR technology
- Checkpoint molecule inhibitors
  - CTLA-4, PD-1 - mAbs
  - Results in significantly increased spontaneous T cell anti-tumor immunity
  - No veterinary use to date
- T regulatory cell depletion
  - mAb technology?
- New vaccines!
  - CSPG-4 vaccine for melanoma
References


Questions?